4.0 HUMAN HEALTH TOXICITY ASSESSMENT

The purpose of the toxicity assessment is to weigh the available and relevant evidence regarding the potential for chemicals to cause adverse health effects to exposed individuals, and to provide a quantitative estimate of the relationship between the magnitude of exposure and the likelihood of adverse effects (USEPA 1989). This section summarizes the potential toxic effects of each chemical of concern as well as the relevant toxicity criteria that are used to assess the risks associated with the dose of the COPCs. A fundamental principle of toxicology is that the dose determines the severity of the effect. Accordingly, the toxicity criteria describe the quantitative relationship between the dose of a chemical and the type and incidence of the toxic effect. This relationship is referred to as the dose-response. The types of toxicity criteria are described below followed by brief discussions of specific criteria and associated health effects for each COPC. More detailed discussions of toxicity criteria for each metal are provided in Appendix H. Table 4-1 and Tables 5.1, 5.2, 6.1 and 6.2 in Appendix A summarize the toxicity criteria used in this assessment.

4.1 ORAL TOXICITY CRITERIA

A dose-response evaluation is the process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of the chemical and the incidence of adverse health effects in the exposed population. From this quantitative dose-response relationship, toxicity criteria are derived that can be used to estimate the potential for adverse health effects as a function of exposure to the chemical. Toxicity values are combined with the summary intake factors calculated in Section 3 and are used to calculate human risks for various exposure scenarios. Exposure to chemicals can result in cancer or noncancer effects, which are characterized separately. Essential dose-response criteria are the EPA slope factor (SF) values for assessing cancer risks and the EPA-verified RfD values for evaluating noncancer effects. These criteria are from the EPA's online database, Integrated Risk Information System (IRIS) (USEPA 2000a). Where IRIS criteria were not available (only iron), other EPA sources of toxicity criteria were investigated.

4.1.1 Cancer Effects

The cancer SF (in units of $(mg/kg\text{-}day)^{-1}$) expresses excess cancer risk as a function of dose. The dose-response model is based on high- to low-dose extrapolation, and assumes that there is no lower threshold for the initiation of toxic effects. Specifically, cancer effects observed at high doses in laboratory animals or from occupational or epidemiological studies are extrapolated, using mathematical models, to low doses common to environmental exposures. These models are essentially linear at low doses, such that no dose is without some risk of cancer. SFs have been developed by the EPA for both the oral (ingestion) and inhalation routes of exposure. Only oral SFs were used in the HHRA Report.

The SF for arsenic, the only established human carcinogen evaluated in this risk assessment, is based on human epidemiologic studies and real environmental exposures. The EPA has classified arsenic as a

proven human carcinogen. Some of the other metals of concern are classified as a probable or possible human carcinogen by EPA, but human data are limited or inadequate to classify them as a known (or proven) human carcinogen. Therefore, there are no corresponding Cancer Slope Factors for these COPCs, and a quantitative evaluation of possible associated cancers risk is not possible.

4.1.2 Noncancer Effects

Chronic RfDs are defined as an estimate of a daily exposure level for the human population, including sensitive populations, that is likely to be without appreciable risk of noncancer effects during a lifetime of exposure (USEPA 1989). Chronic RfDs are specifically developed to be protective for long-term exposure to a chemical and are generally used to evaluate the potential noncancer effects associated with exposure periods of 7 years to a lifetime. RfDs are expressed as mg/kg-day and are calculated using lifetime average body weight and intake assumptions.

RfD values are derived from experimental data on the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) in animals or humans. The NOAEL is the highest tested chemical dose given to animals or humans that has not been associated with any adverse health effects. The LOAEL is the lowest chemical dose at which health effects have been reported. RfDs are calculated by dividing the NOAEL or LOAEL by a total uncertainty factor, which represents a combination of individual factors for various sources of uncertainty associated with the database for a particular chemical or with the extrapolation of animal data to humans. RfDs and associated uncertainty factors for each chemical are discussed in Section 4.3. IRIS also assigns a level of confidence in the RfD. The level of confidence is rated as either high, medium, or low based on confidence in the study and in the database. RfDs have been developed by the EPA for both the oral (ingestion) and inhalation routes of exposure. Only oral RfDs were used in this HHRA.

4.2 DERMAL TOXICITY CRITERIA

Only arsenic and cadmium were evaluated for dermal toxicity in this risk assessment because scientific support for dermal toxicity for the other metals is inadequate (USEPA 1999c). There are no available RfDs or SFs specifically for dermal exposures. Risks and hazards associated with dermal exposure are evaluated using an oral toxicity factor corrected for percutaneous absorption. This route-to-route extrapolation assumes that on the basis of absorbed (as opposed to administered) dose, the toxicity of a hazardous constituent is the same once it enters the blood, regardless of the actual route of exposure. The administered dose is the amount that is presented to a person's "exchange surfaces" or points of contact with the external world, including the mouth, skin, and nose. The absorbed dose is the fraction of the administered dose that actually enters the body's general circulation. Because the skin forms an effective barrier to many chemicals, only a fraction of the dose administered on the skin's surface will be absorbed through the skin into the bloodstream.

The chronic RfD for arsenic was not adjusted from an administered dose to an absorbed dose because the RfD is based on the NOAEL for skin effects from a study involving arsenic exposures to more than

40,000 people in Taiwan. These people were exposed for a significant portion of their lifetime to arsenic-contaminated groundwater used as drinking water. Because most arsenic ingested in water is absorbed through the gastrointestinal tract, the administered RfD is a good approximation of the orally absorbed dose (USEPA 2000a). For cadmium, the administered oral RfD of 0.001 mg/kg-day (food) was multiplied by a gastrointestinal fraction of 2.5 percent to derive the dermal RfD of 0.000025 mg/kg-day (USEPA 2000a).

4.3 CHEMICAL PROFILES

Toxic effects of the chemicals of concern are summarized in the following subsections along with the toxicity criteria for assessing noncancer and cancer effects. In general, the information has been summarized from the latest available ATSDR profile for each chemical and the information is provided in Appendix H.

4.3.1 Antimony

Antimony is found at low concentrations in soil, generally 1 mg/kg or less. The geochemical properties of antimony are similar to those of arsenic (i.e., antimony has +3 and +5 valence states). As with arsenic, antimony may be associated with nonferrous ore deposits and, therefore, can be a pollutant in industrial environments. Antimony is a constituent in alloys with nonferrous metals such as tin, lead, and copper. Sulfides are used in the production of rubber and pyrotechnics. Chlorides are used as coloring agents and catalysts.

Antimony is poorly absorbed from the gastrointestinal tract. Acute exposure by ingestion is irritating to the gastrointestinal tract. Long-term ingestion exposure in laboratory animals has been associated with changes in blood chemistry, including increased serum cholesterol and decreased nonfasting serum glucose levels. The issue of bioavailability of antimony in soil is important because antimony often exists, at least in part, as a poorly soluble salt and may also occur in particles of inert or insoluble material. These factors all tend to reduce the bioavailability of antimony.

Inhalation of antimony compounds has been reported to be toxic to smelter workers, producing effects in both the respiratory and gastrointestinal tract. Inhalation exposure in workers may also be associated with effects on the cardiovascular system (elevated blood pressure) and pneumoconiosis, including interstitial inflammation leading to fibrosis of the lung and altered pulmonary function.

There is inconclusive evidence of a relationship between the inhalation of antimony trioxide and excess risk of lung cancer and reproductive disorders. Cancer evidence from studies in human populations is very limited, and carcinogenicity studies in laboratory animals provide conflicting results.

The oral RfD for antimony of 0.0004 mg/kg-day is based on decreases in nonfasting blood glucose levels, altered cholesterol levels, and decreased longevity in rats administered antimony in drinking water at a concentration of 5 µg/L for life. The RfC of 0.0002 mg/m^3 has been developed specifically

for antimony trioxide and is based on the occurrence of chronic interstitial inflammation in the lungs and reduced clearance of inhaled particulates in rats exposed by inhalation for 1 year.

4.3.2 Arsenic

Arsenic trioxide is the most commercially important form of arsenic and is produced primarily from flue dust that is generated at copper and lead smelters. The principal use of arsenic (as arsenic trioxide) is in wood preservatives and a smaller proportion is used in the production of agricultural chemicals such as insecticides, herbicides, algaecides, and growth stimulants for plants and animals. The use of many arsenical pesticides has been phased out because of concerns about human health risks during production or use. Arsenic trioxide is no longer produced in the United States. Smaller amounts of arsenic are used in the production of glass and nonferrous alloys and in the semiconductor industry.

Arsenic has been shown to be toxic to human populations in areas of the world where it is present at naturally elevated concentrations in groundwater and to occupationally exposed workers in copper smelters and chemical plants. There is strong evidence that arsenic is carcinogenic in humans by both oral and inhalation routes. Arsenic occurs in soil and rock along with other minerals such as copper, lead, iron, and nickel. It is typically found in soil in the form of an insoluble sulfide. Naturally occurring arsenic concentrations in soil range from 1 to 40 mg/kg, with a mean concentration of approximately 5 mg/kg. Naturally occurring arsenic concentrations in groundwater average around 1 to 2 µg/L, except for some western states with geological features that have naturally elevated concentrations of arsenic. Concentrations in groundwater in these areas range from 5 to more than 500 µg/L. In the United States, over 350,000 people may drink water containing arsenic concentrations higher than the current MCL of 50 µg/L. USEPA has promulgated a new MCL for arsenic of 10 µg/L and estimated over 12 million people may be drinking water containing arsenic at concentrations above 10 µg/L (Federal Register 2001). The USGS estimates that 40% of both large and small water supplies have arsenic concentrations greater than 1 µg/L (Welch et al. 1999).

Inorganic arsenic (the form typically found in soil or water) is often in a form that is readily absorbed either by ingestion or by inhalation. Following absorption, it is distributed throughout the body. Studies with laboratory animals suggest that the bioavailability of arsenic in soil may be lower than that of arsenic ingested in solution. The issue of arsenic bioavailability is especially important at mining, milling, and smelting sites because the arsenic at these sites often exists, at least in part, as a poorly soluble sulfide and may also occur in particles of inert or insoluble material. These factors all tend to reduce the bioavailability of arsenic (See discussion for arsenic's gastrointestinal absorption factor in Section 3.3.3).

Arsenic is partly metabolized in the liver by methylation (the metabolic addition of methyl groups to inorganic arsenic ions), converting inorganic arsenic into methyl- and dimethylarsenic compounds. Absorbed organic and inorganic arsenic compounds are principally excreted in the urine. Methylation followed by urinary excretion has been considered a detoxification mechanism for inorganic arsenic. However, a recent study by Mass et al. (2001) found that methylated trivalent arsenic added to human

peripheral lymphocytes produced direct DNA damage. These findings indicate that biomethylation of absorbed inorganic arsenic is not solely a detoxification pathway (see also a further discussion in the uncertainty section).

Several organic arsenicals have been found to accumulate in fish and shellfish. These derivatives (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") have been studied by several researchers and have been found to be essentially nontoxic.

Arsenic at high levels of exposure is irritating to the gastrointestinal tract. Common symptoms in humans after acute high-dose ingestion of inorganic arsenic compounds are nausea, vomiting, and diarrhea. Signs of peripheral neuropathy have been noted in individuals who have ingested inorganic arsenic. The neuropathy is detected as numbness in the hands and feet, progressing to a painful "pins and needles" sensation. Acute lethality from arsenic ingestion is usually attributed to cardiopulmonary collapse.

Evidence of reproductive or developmental toxicity in humans is limited. However, a recent study (Hopenhayn-Rich et al.2000) found, in a retrospective analysis of a Chilean city with formerly high water arsenic levels, that there were significant associations between late fetal mortality rates, neonatal mortality rates, and postnatal mortality rates and the concurrent water arsenic concentrations. These data support a role for water arsenic levels increasing late fetal and infant mortality (Hopenhayn-Rich et al.2000). Studies in laboratory animals suggest that arsenic produces developmental toxicity (reduced birth weight, fetal malformations, and increased fetal mortality) at high levels of exposure. The data suggest that inorganic arsenic does not pose a significant risk of developmental toxicity except at levels that would cause toxic effects on the mother (i.e., maternally toxic doses) (Holson et al. 2000, ATSDR 1993).

Arsenic has been associated with adverse effects on human populations in different parts of the world, which were exposed to levels in drinking water exceeding 300 µg/L over a long period of time. Two recent studies (Kurtio et al. 1999, Chiou et al. 2001) found a statistically significant increased risk of bladder cancer at drinking water levels well below 300 µg/L at 0.5 µg/L and 10-50 µg/L for the Finnish and Taiwan studies, respectively (see also uncertainty section).

The distinguishing adverse effects associated with chronic ingestion of arsenic are skin lesions (hyperkeratoses and hyperpigmentation) and skin cancer. Other adverse effects due to ingestion exposure include cancer of the internal organs (prostate, liver, bladder, and kidney) and a vascular disease known as "blackfoot disease" (Blackfoot disease has been observed only in an area of Taiwan where there are naturally elevated arsenic concentrations in drinking water). Occupational exposure (principally copper smelter workers) has been associated with an increased incidence of lung cancer. The EPA has given arsenic a carcinogenicity weight-of-evidence classification of a Group-A (human carcinogen) based on sufficient evidence of cancer mortality from both ingestion and inhalation exposures in human populations. The International Agency for Research on Cancer classifies arsenic as a proven human carcinogen.

Some information about human populations that may be sensitive to arsenic exposure has been identified. Individuals with impaired liver function or poor nutritional status may not detoxify arsenic efficiently and may be at greater risk of adverse effects from arsenic exposure. In addition according to current data, children are sensitive to arsenic for two reasons. First, two studies have shown that children do not biomethylate arsenic as well as adults (although this may make them less sensitive to cancer effects noted in the recent Mass et al. study described above), i.e., they are at higher risk for noncancer effects and to some extent cancer effects from the higher net fraction of inorganic arsenic (Kurttio et al. 1998; Concha, Nermell, and Vahter 1998a). Second, there has been a recent finding that children appear to be more sensitive for response when one looks at biomarkers that are specific for certain carcinogens. Tang et al. (1999) reported that compared to adults, children have higher circulating levels of a key biomarker for carcinogenic substances from environmental tobacco smoke. Pregnant women have also been identified as a sensitive population. It has been shown that arsenic crosses the placental barrier (Concha et al. 1998b, NRC 1999), and in pregnant women exposed to arsenic, blood arsenic levels in the newborns are almost as high as the level in cord blood. Food and drinking water are the largest sources of arsenic exposure. Studies in laboratory animals suggest that low levels of dietary arsenic may be beneficial or essential. However, there is no known specific biochemical mechanism by which arsenic could exert a beneficial effect. If arsenic is beneficial to humans, then the daily requirement is probably met by normal dietary intake.

The EPA has promulgated a new MCL for arsenic based on recent epidemiological findings associating arsenic exposure with an increase in internal organ cancers. At the request of the EPA, the National Academy of Sciences (NAS) reviewed the current state of science for estimating risks associated with arsenic in drinking water. In its review, completed in 1999, the NAS recommended lowering the MCL from the current interim drinking water standard of 50 µg/L. This recommendation is based on NAS's assessments of the risks of skin, lung, and bladder cancer from drinking water containing inorganic arsenic (NRC 1999). The EPA published a final rule lowering the MCL from 50 µg/L to 10 µg/L (Federal Register 2001). In addition to information from the NRC's report, the EPA also considered a recent epidemiological study in Utah (Lewis et al. 1999) when proposing the new MCL. The Utah study found a significant increase in hypertensive heart disease among males and females, although no dose-response trend was noted between the low, medium, and high exposure groups for this disease end point. Cardiovascular effects of arsenic have been documented in a number of other studies at higher arsenic concentrations than the 4 Fg/L to 620 Fg/L reported in the Utah study (median exposure concentration <200 Fg/L). The Utah study also found a statistically significant increase in prostate cancer and nephritis/nephrosis among study males. Prostate cancer has not previously been associated with arsenic; however, other studies have noted kidney problems, see further discussion in the uncertainty section. While the Utah population is likely not representative of the United States population in general, the EPA considers this study to provide further weight to concerns about arsenic health effects in drinking water at concentrations below the current MCL. The Utah study is of particular interest because of the relatively low range of arsenic water concentrations in contrast to other epidemiologic studies which generally had average arsenic exposure in the several hundreds µg/L range. In addition, the Utah study suggested that cardiovascular effects can occur at lower levels than those seen in the studies reviewed by NRC. The Utah study is further discussed in section 7.

The oral RfD for arsenic is based on the occurrence of hyperpigmentation and hyperkeratosis and vascular complications observed in the Taiwanese population ingesting elevated levels of arsenic in drinking water. The NOAEL was calculated to be 0.0008 mg/kg-day. An uncertainty factor of 3 is applied to account for both (1) the lack of data to preclude reproductive toxicity as a critical effect, and (2) some uncertainty pertaining to whether the NOAEL of the critical study accounts for all sensitive individuals. The oral RfD for arsenic is 0.0003 mg/kg-day. According to the EPA, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.0001 to 0.0008 mg/kg-day. An inhalation RfD or reference concentration (RfC) has not been estimated for arsenic (USEPA 2000a).

The oral unit risk factor for estimating excess lifetime cancer risks is based on the incidence of skin cancer observed in the Taiwanese population ingesting elevated levels of arsenic in drinking water. Doses were converted to equivalent doses for males and females in the United States based on differences in body weights and differences in water consumption. It was assumed that skin cancer risk in the U.S. population would be similar to that in the Taiwanese population. The maximum likelihood estimate (MLE) of skin cancer risk for a 70-kg person drinking 2 L of water per day ranged from 1 x 10^{-3} to 2 x 10^{-3} for an arsenic intake of 1 µg/kg-day. Expressed as a single value, the cancer unit risk for drinking water is 5 x 10^{-5} L/µg. Details of the assessment are in USEPA (1988) (USEPA 2000a). Using the assumptions of 2 L/day drinking water consumption and 70-kg body weight, this unit risk factor converts to an oral SF of 1.5 $(mg/kg\text{-}day)^{-1}$. It should be noted that the EPA's assessment is based on Taiwanese data on the prevalence of skin cancer from the IRIS database. However, arsenic has also been associated with internal organ cancers, particularly lung and bladder cancer (NRC 1999, Federal Register 2001). Recent epidemiological data from South America indicate that risks based on fatal internal cancer could be an order of magnitude higher than risks based on skin cancer. Thus, risks calculated from IRIS could be underestimated. See Section 7 for a more detailed discussion. NRC 1999 estimated that the combined risk for bladder and lung cancer could be as high as 1 in 100 at arsenic's previous MCL of 50 ppb.

4.3.3 Cadmium

Cadmium is obtained mainly as a by-product during the processing of zinc-bearing ores and also from the refining of lead and copper from sulfide ores. Cadmium is used primarily for the production of nickel-cadmium batteries, in metal plating, and for the production of pigments, plastics, synthetics and metallic alloys. Cadmium has been shown to be toxic to human populations from occupational inhalation exposure and accidental ingestion of cadmium-contaminated food. Inhalation of cadmium dust in certain occupational settings may be associated with an increased incidence of lung cancer. Ingestion of elevated levels of cadmium has resulted in toxicity to the kidney and skeletal system and may be associated with an elevated incidence of hypertension and cardiovascular disease.

Cadmium is poorly absorbed from the lung, gastrointestinal tract, and skin. Individuals with dietary deficiencies of iron, calcium, or protein exhibit higher absorption of ingested cadmium. The issue of cadmium bioavailability is especially important at mining, milling, and smelting sites because the

cadmium at these sites often exists, at least in part, as a poorly soluble sulfide and may also occur in particles of inert or insoluble material. These factors all tend to reduce the bioavailability of cadmium in soil. Cadmium in the body binds readily to certain sulfur-containing proteins, such as metallothionein. Binding to metallothionein is thought to reduce the toxicity of cadmium. Following ingestion, fecal excretion is high due to poor gastrointestinal absorption. Most cadmium that has been absorbed, however, is excreted very slowly, with fecal and urinary excretion being about equal. Urinary cadmium levels are an indicator of body burden, i.e., chronic exposure.

Much of the understanding about cadmium toxicity in humans is based on epidemiological studies of human populations. Humans consuming cadmium-contaminated rice in Japan developed kidney and skeletal system effects. Inhalation of cadmium in occupational settings has also been associated with kidney toxicity. There is conflicting evidence as to whether or not cadmium exposure produces cardiovascular effects or hypertension in humans; factors such as cigarette smoking are confounders in determining the relationship between cadmium exposure and cardiovascular effects. Excessive cadmium ingestion exposure in combination with a low dietary intake of iron may be associated with anemia.

Ingested cadmium is not known to be carcinogenic in humans. Studies in laboratory animals generally do not indicate that cadmium is carcinogenic by ingestion. Inhaled cadmium is carcinogenic to laboratory animals. However, epidemiological studies of cadmium-exposed workers have been inconclusive in demonstrating the carcinogenicity of inhaled cadmium. The EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1) based on limited evidence in humans and sufficient evidence in laboratory animals.

Populations potentially sensitive to cadmium have not been studied systematically; however, it is possible to infer potential sensitivities based on the available data. Individuals with poor nutritional status, particularly in terms of iron and calcium, may absorb more cadmium from the gastrointestinal tract. Individuals with preexisting kidney damage may experience kidney toxicity at cadmium doses lower than the dose that would be toxic for normal individuals.

The EPA recently conducted a toxicological review of cadmium and compounds in support of a proposed revision of the toxicity factors currently listed in IRIS. However, the report is currently undergoing external review and the proposed toxicity factors have not been finalized.

The current EPA recommendation consists of two oral RfDs for cadmium, one for cadmium exposure from food and one for cadmium exposure from water. Both RfDs recognize that a concentration of 200 µg/g (wet weight) in the human kidney cortex is the highest renal level not associated with significant proteinuria. A toxicokinetic model was used by the EPA to determine the level of chronic human oral exposure (NOAEL) that results in the critical concentration of cadmium in the kidney of 200 µg/g; the model assumes that 0.01 percent of the cadmium body burden is eliminated per day (USEPA 1985). Assuming 2.5 percent absorption of cadmium from food or 5 percent from water, the toxicokinetic model predicts that the NOAEL for chronic cadmium exposure is 0.005 and 0.01 mg/kg-

day from water and food, respectively (i.e., the doses corresponding to the 200 µg/g critical kidney concentration). An uncertainty factor of 10 to account for intrahuman variability was applied to these NOAELs to obtain an RfD of 0.0005 mg/kg-day (water) and an RfD of 0.001 mg/kg-day (food) (USEPA 2000a). No inhalation RfD or RfC is currently listed for cadmium. A dermal RfD of 0.001 mg/kg-day multiplied by 2.5 percent (0.000025 mg/kg-day) was selected for use in the calculations.

The critical toxic effect proposed for both the oral RfD and inhalation RfC is renal dysfunction, as indicated by minimal proteinuria/enzymuria. This critical effect is supported by the results of several cross-sectional population studies, especially the CadmiBel population study of Buchet et al. (1990). The CadmiBel study authors (Lauwerys et al., 1993) found that the critical kidney cortex level of cadmium in the general population was 50 ppm, four-fold lower than that found in mainly healthy workers, 200 ppm. This difference is not unexpected, in that general population data include more of a range of inter-individual health status including those with poor health. A toxicokinetic model was used with the data in this study to calculate both a daily oral intake and a continuous air concentration of cadmium that would result in a 10 percent occurrence of minimal enzymuria (the critical effect) in the population at the age of 70. A representative level of dietary cadmium intake was integrated into the toxicokinetic model. The net oral intake (model result minus diet) of 0.0007 mg/kg-day was designated the oral RfD. USEPA (1999f) has proposed that one RfD be used for oral exposures to all media (i.e., separate RfDs were not proposed for ingestion of cadmium in food or water). The modeled concentration of cadmium inhaled concomitant with this same representative dietary intake was designated as the inhalation RfC of 0.0007 mg/m^3. For both the RfD and the RfC, alternate contributions of intake from background (and therefore different RfDs and RfCs) are described in EPA's toxicological review (USEPA 1999f).

4.3.4 Iron

Iron is a major constituent in rocks and soil. In combination with carbon, manganese, chromium, nickel, and other elements, it is used in the manufacture of steel. Iron is an essential element in human nutrition; however, there is the potential for adverse health effects principally from excessive ingestion exposure.

The absorption of iron and its distribution in the body are closely regulated to maintain homeostasis. Absorption of iron from the diet ranges between 2 and 15 percent, with increased absorption during times of greater need, such as childhood, pregnancy, or following blood loss. Iron is found mostly in hemoglobin in red blood cells; however, it can also be stored in the liver and spleen. Excretion of iron from the body is fairly limited. Excess iron is bound to proteins and stored primarily in the liver.

The issue of iron bioavailability is especially important when considering soil exposure pathways because iron in soil can exist, at least in part, as poorly soluble salts and may also occur in particles of inert or insoluble material. These factors all tend to reduce the bioavailability of iron.

Severe acute toxicity has resulted from the accidental ingestion of iron-containing medications, principally by children eating ferrous sulfate tablets with candy-like coatings. Signs of overexposure include ulceration of the gastrointestinal tract with vomiting (including blood), black stools, damage to the liver and kidneys, and metabolic acidosis. Death from exposure to iron is thought to occur from renal failure and cirrhosis of the liver.

Chronic overexposure (also known as iron overload) may occur as a result of excessive dietary consumption of iron or from a condition known as idiopathic hemochromatosis. Chronic overexposure results in excess iron accumulation in the liver, spleen, pancreas, endocrine organs, and the heart. Adverse effects may include disturbance of liver function, diabetes mellitus, disturbance of endocrine function, and cardiovascular effects. On a cellular level, increased lipid peroxidation occurs, resulting in damage to the membranes of cell organelles. Although there are no known sensitive populations for exposure to iron, idiopathic hemochromatosis is thought to have a genetic component.

Years of inhalation of iron oxide fumes or dust causes a benign pneumoconiosis in miners and metal workers referred to as siderosis, which generally does not result in reduced pulmonary function. An increased incidence of lung cancer has been observed among hematite miners and iron workers who have been exposed to iron oxide. However, there may be other factors to explain the observed cancer incidence, including exposure to other carcinogens such as cigarette smoke, radon, and polycyclic aromatic hydrocarbons, or exposure to silica dust.

While iron generally is not considered to be carcinogenic or mutagenic, excess iron can result in lipid peroxidation, which may result in genotoxic effects, such as damage to DNA or chromosomes. In studies with laboratory animals, iron overload may potentiate the effects of other carcinogens. Elevated exposure to iron is not considered to be associated with reproductive or developmental toxicity.

The EPA's IRIS database does not currently provide an RfD, cancer SF, or other toxicological information for iron (USEPA 2000a). The EPA Superfund Technical Support Center has developed a provisional oral RfD for iron. The EPA notes that iron is an essential nutrient and that deriving a risk assessment value for it poses special problems in that the dose-response curve is U-shaped (i.e., there is a range of doses necessary to maintain health; doses both above and below that range can result in adverse effects). Thus, the provisional RfD must be protective against deficiency as well as toxicity. A NOAEL for chronic iron overload has been estimated using the values for dietary intake and iron status indices taken from the NHANES II database (USEPA 1999e). Looker et al. (1988) compared dietary iron intakes with biochemical indices of iron status using data from NHANES II. The average intakes of iron ranged from 0.15 to 0.27 mg/kg-day. The serum ferritin levels and percent serum transferritin saturation (both indicators of iron overload) were within the normal range. Thus, iron intake levels of 0.15 to 0.27 mg/kg-day are considered both sufficient to protect against iron deficiency and insufficient to cause the toxic effects of iron overload.

Using the NOAEL of 0.27 mg/kg-day (representing the upper bound value in the range of mean dietary iron intakes, dietary plus supplemental, taken from the NHANES II database) and dividing by an

uncertainty factor of 1 yields the provisional chronic oral RfD of 0.3 mg/kg-day. An uncertainty factor of 1 is supported by the fact that iron is an essential nutrient. In addition, the oral RfD for iron was derived from intake data from over 20,000 individuals aged 6 months to 74 years and humans exert an efficient homeostatic control over iron such that body burdens are kept constant with normal variations in diet. This RfD supplies adequate levels of iron to meet the nutritional requirements of adults and adolescents. It does not supply the recommended dietary allowance (RDA) for members of the population with greater requirements for shorter-than-lifetime durations, including children and pregnant women. Further, this RfD may not be protective of individuals with inherited disorders of iron metabolism and could be conservative if applied to exposure scenarios involving forms of iron with low bioavailability (USEPA 1999e).

4.3.5 Lead

Lead is a soft, bluish-gray metal. Lead acetate and lead nitrate are soluble in water; lead chloride is slightly soluble; and lead sulfide, lead phosphate, and lead oxides are not soluble in water. Some primary uses of lead in the United States are in lead-acid storage batteries, ammunition, bearing metals, brass, bronze, cable covering, extruded products, sheet lead, solder, ceramics, type metal, ballast or weights, tubes or containers, oxides, and gasoline additives.

Substantial quantities of both human and animal data are available regarding the toxicity of lead. This toxicity profile relies primarily on human data. Adverse effects of lead in humans are most often related to the blood lead level as an indicator of internal lead dose. Therefore, whenever possible, this text relates adverse effects to blood lead levels rather than to external exposure. The Centers for Disease Control (CDC) have based policy on primary and secondary childhood lead prevention activities on the association of certain adverse health effects with different blood lead levels. Tables 4-2 and 4-3 summarize the lowest-observed-effect levels (LOELs) (expressed as PbB levels) for key lead health effects in children and adults, based on information in NRC and CDC (1993;1991). Section 6.2.1 describe the CDC primary and secondary prevention guidelines regarding childhood blood lead levels.

Lead absorption is influenced by the route of exposure, the exposure medium, speciation and physiochemical characteristics of lead, and the age and physiological state of the exposed individual. Approximately 30 to 50 percent of airborne particulate lead is absorbed. Children 2 weeks to 8 years of age absorb about 40 to 50 percent of ingested lead. A study using Bunker Hill soils found nonfasted adults absorbed 2.5 percent of lead ingested in soil and fasted adults absorbed 26.2% of lead ingested in soil (Maddaloni et al. 1998). The amount of lead absorbed from the skin in humans is unknown.

Lead is absorbed into blood, where about 99 percent of it is located in red blood cells. Lead in blood rapidly exchanges with lead in other soft tissues. Bone contains about 94 percent and 73 percent of total lead body burden in adults and children, respectively. The average half-life for lead is 28 to 36 days in blood, about 40 days in soft tissues, and about 27 years in bone. Lead in bone can be mobilized into maternal blood during pregnancy and lactation. Lead in maternal blood is efficiently transported to the fetus, and breast milk can be a significant source of lead for breast-feeding infants.

Lead in the gastrointestinal tract that is not absorbed is eliminated in the feces. Absorbed lead that is not retained is eliminated in the urine or excreted in the feces following biliary secretion into the gastrointestinal tract.

Death from encephalopathy has been reported in children and adults with very high blood lead levels (e.g., 80-100 Fg/dl). There is conflicting evidence in occupational mortality studies of chronic lead exposure. IQ decrements, fine-motor dysfunction, altered behavior, peripheral neuropathy, and reduced motor nerve conduction have been reported in children. A threshold below which lead does not affect IQ in children has not been identified. Decreased hearing thresholds and alterations in the electrical activity of the brain have also been observed in children. Lead can also induce neurotoxicity in adults, including encephalopathy, overt neurological signs, decreased scores on neurobehavioral tests, and decreased motor nerve conduction.

Lead interferes with heme synthesis. Reduction of the heme body pool can lead to adverse effects in several physiological systems. Anemia can result from decreased hemoglobin production and increased red blood cell destruction. Lead-induced inhibition of heme synthesis can interfere with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. There is no apparent threshold for indicators of decreased heme synthesis.

Acute, generally reversible, nephropathy can occur during the early stages of high exposure to lead. Chronic (irreversible) nephropathy can also occur. Acute exposures to high levels of lead can produce cardiac lesions, electrocardiographic abnormalities, and hemolytic anemia in children and adults. There is conflicting evidence regarding the potential effects of blood lead levels on blood pressure in adults. Colic is a relatively late symptom of severe or clinical lead poisoning generally observed at blood lead levels greater than 50 Fg/dl.

Women with occupational exposures to lead during pregnancy have an increased rate of miscarriages and stillbirths. There is no evidence of teratogenic effects in humans or animals due to exposure to low levels of lead. There is conflicting information regarding the potential effects of lead on birth weight, gestational age, and growth in children. There is conflicting evidence regarding the potential effects of lead on human chromosomes. In men with occupational exposures some reproductive effects (e.g., decreased sperm count, abnormal sperm morphology, decreased sperm mobility, and hormonal changes) can occur at blood lead levels of 40 Fg/dl or greater.

Although lead is considered to be carcinogenic in animals with the endpoint being renal cancer, evidence of its carcinogenicity in humans is generally considered to be inadequate. EPA's IRIS database classifies lead as a probable human carcinogen (Group B2), based on sufficient evidence in animals, but inadequate evidence in humans. Lead carcinogenicity will not be evaluated quantitatively in this risk assessment.

Sensitive members of the population can include developing embryos/fetuses/neonates, young children, women, and individuals with chronic neurological dysfunction or kidney disease. Older adults are at

risk for lead-associated hypertension (NRC 1993). The embryo/fetus/neonate may be at increased risk due to the effects of lead because of a developing nervous system that is more sensitive to the effects of lead and the transfer of maternal lead during pregnancy and lactation. Young children may be especially at risk because compared to adults they absorb more lead from the gastrointestinal tract; retain more absorbed lead; have a greater prevalence of nutritional deficiencies (e.g., calcium, iron, and zinc), which can increase both the absorption and the toxic effects of lead; have an incompletely developed blood-brain barrier; have a developing nervous system that is more sensitive to the effects of lead; ingest much more soil/dust per kg body weight, ingest more water per kg body weight; and inhale more air per kg body weight. Women who are pregnant, are lactating, or have osteoporosis may be themselves at greater risk due to lead because each of these conditions may intensify the mobilization of lead from bone.

Blood lead level is the easiest and most widely used index of lead exposure and toxicity. Blood lead primarily reflects recent exposure for lead but can also reflect, to a lesser extent, the body burden of lead, which is more related to long-term exposure. For children and fetuses, 10 µg/dl is generally considered a blood lead level of concern (CDC 1997; CDC 1991). There is less agreement on a single blood lead level of concern for male adults and nonpregnant female adults, but estimates fall within the range of 25 to 40 µg/dl. However, analysis of U.S. NHANES II epidemiological data (NAS 1993) shows hypertensive effects in the form of elevated systolic and diastolic blood pressure in older adults at blood lead values well below this range.

A number of pharmacokinetic models for lead are available to predict blood lead levels based on lead intake in various exposure media (USEPA 1994a, 1996c; CalEPA 1992, 1996; O'Flaherty 1998; Leggett 1993; Bowers, Beck, and Karam 1994; ATSDR 1999b). The EPA models (USEPA 1994a, 1996c) are typically used at Superfund sites to evaluate risk to adults or children from exposure to environmental lead.

The toxic effects of lead are generally considered to be similar regardless of the route of entry. Most adverse effects of lead have been related to lead in blood and (to a lesser extent) tooth dentin (Tables 4-2 and 4-3). There are relatively few data relating human health effects to exposure-route specific external exposure (e.g., mg/kg-day or m^3/day).

Ingestion is the primary route of exposure for children and other non-occupationally exposed individuals. However, dose-response data based on external ingestion dose (mg/kg-day) in humans were limited. Hematological effects were observed in adult humans who ingested 0.02 to 0.03 mg lead acetate/kg-day for 14 days or 0.01 to 0.02 mg lead acetate/kg-day for 3 to 7 weeks.

Inhalation is an important route of exposure for adults at work. However, very little dose-response data in workers using lead air concentrations (mg/m^3) were located. A 47 percent decrease in ALAD activity was observed in men inhaling lead at a concentration of 0.011 mg/m^3 for 18 weeks.

ATSDR (1999b) reported that no studies were located regarding toxicity of lead in humans or animals specifically from dermal exposure. Dermally applied lead nitrate is rapidly absorbed by the skin, but the toxicology significance is unknown.

4.3.6 Manganese

Manganese is an essential element in human nutrition, serving as a cofactor in several enzymatic reactions. When ingested, manganese is considered to be among the least toxic of the trace elements. The adverse health effects from manganese are principally associated with inhalation exposure in the workplace. Acute inhalation exposure can produce irritation of the respiratory tract. Chronic inhalation exposure can produce a central nervous system disorder resembling Parkinsonism, known as manganism.

Daily intake of manganese ranges from 2 to 9 mg/day. Manganese is poorly absorbed following oral exposure, and reports of human intoxication following ingestion exposures are not common. However, some studies suggest that neurological effects may be associated with the consumption of drinking water with elevated levels of manganese. Although ingestion exposure studies suggest that manganese may be weakly carcinogenic in laboratory animals, these data are inadequate to support a classification as carcinogenic by the EPA. The EPA has categorized manganese as "not classifiable with regard to human carcinogenicity" (Group D).

Several studies have shown that inhalation of manganese in occupational settings is associated with neurological effects. The principal signs of manganism include tremors, weakness in the legs, staggering gait, behavioral disorders, slurred speech, and a fixed facial expression. There is no evidence indicating that inhalation exposure to manganese is carcinogenic in humans; however, there is some evidence of male reproductive effects.

Development of the oral RfD for manganese recognizes that disease states in humans have been associated with both deficiencies and excessive intakes of manganese. The oral RfD for manganese is set at 10 mg/day (0.14 mg/kg-day) and is based on the upper end of the normal dietary intake rate. This value is considered a NOAEL for dietary intake and has not been adjusted by an uncertainty factor. The EPA emphasizes that individual requirements for, as well as adverse reactions to, manganese may be highly variable. The RfD is estimated to be an intake for the general population that is not associated with adverse health effects; this is not meant to imply that intakes above the RfD are necessarily associated with toxicity (USEPA 2000a).

The oral RfD for manganese was evaluated further in other media (drinking water or soil) based on an epidemiological study of manganese in drinking water (USEPA 2000a). Whereas the results from this study do not allow a quantitative evaluation of dose-response, they raise concerns about possible adverse neurological effects at doses not far from the range of essential concentrations. For assessing exposure to manganese from drinking water or soil, USEPA (2000a) recommends adjustment by an uncertainty factor of 3, yielding an oral RfD of 0.047 mg/kg-day. Four reasons are provided for the

use of an uncertainty factor to adjust the oral RfD for soil and water exposure: (1) in fasted individuals, there may be increased uptake of manganese from water; (2) the study raises some concern regarding possible adverse health effects associated with a lifetime consumption of drinking water with manganese concentration of about 2 mg/L; (3) because infant formula typically has a much higher concentration of manganese than that of human milk, manganese in the water could represent an additional source of intake for infants; and (4) neonates may absorb more manganese from the gastrointestinal tract and may be less able to excrete absorbed manganese, and more absorbed manganese may cross their blood-brain barrier.

For this HHRA, an oral RfD of 0.14 mg/kg-day was used to evaluate occupational exposures to manganese in soil. For all other manganese exposures, an oral RfD of 0.047 mg/kg-day was used.

The oral RfDs of 0.047 to 0.14 mg/kg-day and the inhalation RfD of 0.000014 mg/kg-day for manganese (USEPA 2000a) suggest that inhaled manganese may be much more toxic than ingested manganese. Differences in absorption between the two routes cannot alone account for this large difference. The EPA reports that after absorption into blood via the respiratory tract, manganese is transported through the blood stream directly to the brain, bypassing the initial clearance effects of the liver. They state that this pathway from the respiratory tract to the brain is the primary reason for the differential toxicity between inhaled and ingested manganese. In addition, recent studies in animals have shown that manganese has a unique ability among metals to be taken up in the brain via olfactory pathways (Tjalve and Henriksson 1997). This process involves direct diffusion of manganese from the nasal cavity to the central nervous system without entering blood, therefore bypassing both the initial clearance effects of the liver and the blood-brain barrier (Tjalve and Henriksson 1997). This direct pathway to the central nervous system might account in part for the higher toxicity of inhaled manganese.

4.3.7 Mercury

Elemental mercury is a silvery metallic liquid that is volatile at room temperature. Mercury is found in soil and rocks typically as an ore known as cinnabar, consisting of insoluble mercuric sulfide. Concentrations in soil and rock average 0.5 mg/kg, though actual concentrations vary considerably depending upon location. Much of the mercury produced in the United States comes from secondary sources, such as recycling. The largest use of mercury is in the electrolytic production of chlorine and caustic soda. Other uses include electrical devices, switches and batteries, measuring and control instruments, medical and dental applications, and electric lighting.

Mercury has been shown to be toxic to human populations as a result of occupational exposure and accidental ingestion of mercury-contaminated food. The nature of mercury toxicity depends on its chemical form. Accidental ingestion exposure to high levels of organic mercury compounds has produced developmental toxicity in humans.

Ingestion of inorganic mercury, the form most likely to be found in soil, has been associated with kidney toxicity in laboratory animals. The adverse effect of concern associated with soil exposure scenarios, therefore, is likely to be kidney toxicity. Ingestion studies with inorganic mercury suggest cancer effects in laboratory animals. The EPA has classified mercuric chloride and methylmercury as possible human carcinogens (Group C), based on the absence of data in humans and limited evidence of carcinogenicity in animals.

The issue of mercury bioavailability is especially important at mining, milling, and smelting sites because the mercury at these sites often exists, at least in part, as a poorly soluble sulfide and may also occur in particles of inert or insoluble material. These factors all tend to reduce the bioavailability of mercury from soil.

Occupational inhalation exposure to metallic mercury vapor or organic mercury vapor has resulted in neurological effects and kidney toxicity. Toxicity due to inhalation of inorganic mercury salts, the form most likely to be found in soil, has not been studied.

Children are considered a sensitive population for exposure to mercury. Potential differences in sensitivity between children and adults are primarily due to differences in routes of exposure and rates of intake (for example exposure of infants via ingestion of breast milk), greater permeability of the blood-brain barrier in fetuses and infants, and the importance of developmental milestones during childhood exposure periods (such as language or cognitive development). Children also appear to have different patterns of tissue distribution of mercury and methylmercury (i.e., biokinetic patterns) that are different from those of adults.

More recently, the EPA has developed the Mercury Research Strategy to address key scientific questions in order to reduce uncertainties currently limiting its ability to assess and manage mercury and methylmercury risks. This strategy will include evaluations to link toxicity to exposure using a biokinetic model, assessment of sensitive populations, evaluation of recent epidemiological studies, and evaluation of immunological effects.

The EPA has published chronic oral RfDs for mercuric chloride and methyl mercury on its IRIS database (USEPA 2000a). The most sensitive adverse effect for mercuric chloride is reported to be the formation of mercury-induced autoimmune glomerulonephritis. Based on weight of evidence from three subchronic feeding and/or subcutaneous studies in rats, the oral RfD for mercuric chloride is 0.0003 mg/kg-day. All treatment groups exhibited a toxic effect; therefore, a NOAEL was not reported. An uncertainty factor of 1,000 was applied for extrapolations from LOAEL to NOAEL endpoints, subchronic to chronic exposures, and animal to human populations. The EPA reported a high confidence in the oral RfD for mercuric chloride. A subchronic oral RfD of 0.003 mg/kg-day is provided in the Health Effects Assessment Summary Tables (HEAST) for mercuric chloride, based on autoimmune effects observed in rats after subcutaneous injection (USEPA 1997c).

EPA's chronic oral RfD for methyl mercury of 0.0001 mg/kg-day was used to evaluate exposures to mercury in fish (USEPA 2000a). Methyl mercury can be more toxic than mercuric chloride and is likely to be present in fish tissue. Exposures to mercury in all other media were evaluated using the oral RfD for mercuric chloride. Methyl mercury's oral RfD is based on developmental neurologic abnormalities in human infants as determined by epidemiologic studies. An uncertainty factor of 10 has been assigned to this RfD and EPA's confidence in this RfD is medium. A committee of the NAS (NRC 2000) has recently reported its analyses of current human and experimental animal data for methylmercury and has also, as a result, endorsed EPA's methylmercury RfD value of 0.1 µg/dl in its report "Toxicological Effects of Methylmercury" (NRC 2000).

No cancer SFs have been developed for mercury compounds. However, the EPA has classified both mercuric chloride and methylmercury as possible human carcinogens (Group C), based on the absence of data in humans and limited evidence of carcinogenicity in animals, whereas elemental mercury is in Group D (not classifiable due to inadequate data) (USEPA 2000a).

4.3.8 Zinc

Zinc is used in a wide variety of industrial, agricultural, and consumer products. It is found in all human tissues and all body fluids and is essential for growth, development and reproduction. The RDA for zinc is 15 mg, with a slightly higher requirement for pregnant women. Individuals with adequate nutritional levels of zinc absorb approximately 20 to 30 percent of all ingested zinc.

Zinc is usually present in tap water at concentrations less than 0.2 mg/L, although drinking water in galvanized pipes can contain up to 2 to 5 mg/L. Typically, concentrations are much less than the secondary MCL of 5 mg/L, which is based on the threshold for metallic taste in water. An estimate of daily intake of zinc for the adult U.S. population in food is 10 to 20 mg/day.

Gastrointestinal distress is a common symptom following acute oral exposure to zinc compounds. Accidental poisonings have occurred as a result of the use of zinc supplements and from food contamination caused by the use of zinc-galvanized containers. Symptoms develop within 24 hours and include nausea, vomiting, diarrhea, and abdominal cramps. Anemia also may occur in severe cases of acute exposure or in high-dose exposures of longer duration. Inhalation exposure to high concentrations of some zinc compounds (zinc oxide fume) has been associated with "metal fume fever." Attacks of metal fume fever are characterized by chills and fever, weakness, and sweating. Recovery usually occurs within 24 to 48 hours. Zinc chloride, a corrosive inorganic salt, is more damaging to the respiratory tract than zinc oxide. Zinc chloride is a primary ingredient in smoke bombs, and serious respiratory injury has been reported to result from accidental inhalation of smoke from these bombs.

Developmental or reproductive toxicity has been reported in laboratory animals with relatively high levels of exposure to zinc. There is only one unconfirmed report documenting adverse reproductive effects in pregnant women provided zinc supplementation. Other studies in humans conclude there have been no adverse reproductive or developmental effects from exposure to zinc. Genotoxicity

studies have provided very limited evidence of mutagenicity and of weak effects on chromosomes. Available epidemiological studies of human populations and toxicity studies in laboratory animals do not indicate that zinc is carcinogenic. The EPA has given zinc a carcinogenicity weight-of-evidence classification of D (not classifiable as to human carcinogenicity), based on inadequate evidence in humans and laboratory animals.

Zinc interacts with other trace metals and has a protective effect against toxicity from exposure to lead and cadmium. Excessive dietary zinc produces a copper deficiency in laboratory animals. Similar findings have been observed in humans receiving long-term treatment with zinc. No specific data regarding human populations that are unusually susceptible to the toxic effects of zinc have been identified; however, individuals who are malnourished or have a marginal copper status may be more susceptible to the effects of excessive zinc exposure.

The oral RfD is based on a clinical study that investigated the effects of oral zinc supplements on copper and iron balance. A 10-week study of zinc supplementation in 18 healthy women given zinc gluconate supplements twice daily (50 mg zinc/day, or 1.0 mg/kg-day) resulted in a decrease in erythrocyte superoxide dismutase activity. There was a general decline in the mean serum high-density lipoprotein (HDL)-cholesterol in a higher-dose group (receiving 75 mg/day). The EPA has reported that while it is not absolutely certain that the zinc supplementation of 50 mg/day (1.0 mg/kg-day) represents a clearly biologically significant endpoint, this level, when viewed collectively with other studies investigating effects on HDL-cholesterol, may signify the beginning of the dose-response trend (USEPA 2000a). The significance of this change is unknown in light of an absence of increase in low-density lipoproteins (LDLs). An intake of 1.0 mg/kg-day was identified as LOAEL for zinc effects. An uncertainty factor of 3 was used, based on a minimal LOAEL from a moderate-duration study of the most sensitive humans and consideration of a substance that is an essential dietary nutrient. The oral RfD for zinc is 0.3 mg/kg-day (USEPA 2000a).

An RfC or inhalation RfD has not been developed for zinc (USEPA 2000a).